729. *Optical Rotatory Dispersion. Part XV.*[1] *Monosubstituted Succinic Acids*

By A. Fredga, J. P. Jennings, W. Klyne, Patricia M. Scopes, B. Sjöberg, and S. Sjöberg

The optical rotatory dispersion curves of many α-substituted succinic acids have been measured. All these compounds show Cotton effects associated with the carboxyl absorption band at about 225 mμ.

α-Alkyl-, α-aryl-, and α-halogeno-succinic acids of the *D*-configuration all give positive Cotton effects in water and in methanol; *D*-α-alkylthiosuccinic acids give somewhat more complex positive curves. *D*-α-Hydroxysuccinic acid (*D*-malic acid) and its *O*-alkyl ethers give negative Cotton effects in water and in methanol.

The signs of the dispersion curves of most of these acids are *reversed* on the addition of alkali.

Monosubstituted succinic acids have a single centre of asymmetry and are therefore one of the simplest types of compound containing the carboxyl chromophore. Optical rotatory dispersion measurements with acids have previously been confined to wavelengths above about 270 mμ, a region in which these compounds give plain dispersion curves.[2] Automatic recording spectropolarimeters now available permit measurements at shorter wavelengths and Cotton effects associated with the carboxyl chromophore can be observed at about 225 mμ.[3]

The optical rotatory dispersion of a series of monosubstituted succinic acids of known absolute configuration has been examined, and the results obtained in two solvents (water and methanol) are summarised in Table 1. The ultraviolet absorption spectra have also been measured for five compounds, representing the main types of substituents (Table 2). The absorption curves in water all rise steeply at low wavelengths, but each curve has a shoulder or peak at 202—206 mμ which can be ascribed to the carboxyl group. The first extremum of the corresponding Cotton effect occurs at about 220—223 mμ in water and 224—228 mμ in methanol. Measurements of the ultraviolet absorption spectra in methanol below 220 mμ were unreliable owing to end absorption.

In order to facilitate comparisons between compounds, use will frequently be made of such expressions as "the dispersion curve of (+)-X was ......" when, in fact, the material X was the (—)-enantiomer and the signs of rotations have been changed accordingly. The letter E is used to indicate "enantiomer of."

Alkylsuccinic Acids.—The first extremum of the carboxyl Cotton effect has been

---

[1] Part XIV, A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes, and M. J. Vernengo, *J.*, 1965, 2239.

[2] B. Sjöberg, *Acta Chem. Scand.*, 1960, **14**, 273; *Arkiv. Kemi*, 1960, **15**, 451, 481.

[3] J. P. Jennings and W. Klyne, *Biochem. J.*, 1963, 12P; J. P. Jennings, W. Klyne, and P. M. Scopes, *J.*, 1965, 294.

TABLE 1

Optical rotatory dispersion of monosubstituted succinic acids

The values quoted are for the molecular rotation at the first extremum at about 225 mμ or for the lowest wavelength measured if the first extremum was not reached.

pk = Peak; tr = trough; ! = lowest wavelength measured, if *not* an extremum. E, measured as enantiomer.

			H_2O		H_2O–KOH		MeOH		MeOH–KOH	
Acid	Formula	R	[φ]	λ (mμ)	[φ]	λ (mμ)	[φ]	λ (mμ)	[φ]	λ (mμ)
D(+)-Methylsuccinic	I	CH_3	+1205pk	218	−1580tr	220	+1165pk	223	−630!	223
D(+)-Ethylsuccinic	I	C_2H_5	+1680pk	221	−1675!	219	+1490pk	224	−650!	222
D(+)-*n*-Propylsuccinic	I	C_3H_7	+1890pk	222	−1620!	218	+1580pk	224	−570!	222
D(+)-Isopropylsuccinic	I	$(CH_3)_2CH$	+2590pk	223	−510!	222	+2470pk	227	+520!	222
D(+)-*n*-Butylsuccinic	I	C_4H_9	+2045pk	220	−1490!	218	+1600pk	225	−490!	222
D(+)-Isobutylsuccinic	I	$(CH_3)_2CH{\cdot}CH_2$	+1930pk	220	−1675!	222	+1610pk	224	−455!	222
D(+)-*n*-Pentylsuccinic	I	C_5H_{11}	+2180pk	220	−1255!	222	+1740pk	224	−490!	222
D(+)-*n*-Hexylsuccinic	I	C_6H_{13}	+2110pk	220	−1370!	222	+1710pk	226	−305!	225
D(+)-Cyclohexylsuccinic	I	C_6H_{11}	+2840pk	222	−760!	222	+2400pk	228	+500!	222
D(+)-Phenylsuccinic	I	C_6H_5	+13,400pk	228	+9520!	219	+15,450pk	231	+5200!	227
D(+)-Benzylsuccinic (E)	I	$C_6H_5CH_2$	+7910!	223	+6850!	222	+5260pk	227	+455!	226
D(+)-β-Phenylethylsuccinic (E)	I	$C_6H_5(CH_2)_2$	+3810!	222	+450pk	250	+4180!	222	+395!	233
D(+)-γ-Phenylpropylsuccinic	I	$C_6H_5(CH_2)_3$	+2970!	222	+90!	270	+2550!	221	+280!	228
D(−)-Methylglutaric (E)	IV	CH_3	+470!	222	−410!	222	+195!	238	+165!	228
D(−)-Isopropylglutaric	IV	$(CH_3)_2CH$	+730pk	227	+130!	224	+555pk	230	+60!	228
D(+)-Chlorosuccinic (E)	I	Cl	+1215pk	237	−1435!	222	+2200pk	246	−260!	229
D(+)-Bromosuccinic (E)	I	Br	+2765pk	250	+1535pk	248	+2770pk	255	+1475!	245
D(+)-Methylthiosuccinic	I	CH_3S	+3500pk	249	+985pk	240	+3700pk	249	+2020pk	238
D(+)-Ethylthiosuccinic	I	C_2H_5S	+3540pk	248	+1000pk	233	+4560pk	254	+2190pk	240
D(+)-*n*-Propylthiosuccinic	I	C_3H_7S	+3940pk	250	+1025pk	243	+5200pk +5930pk	247 227	+2250pk	244
D(+)-Isopropylthiosuccinic	I	$(CH_3)_2CHS$	+3620 inf.	235	+2340!	228	+5250pk +6000pk	247 227	+4275!	228
D(+)-*n*-Butylthiosuccinic	I	C_4H_9S	+3770pk	251	+1130pk	240	+5310pk	254	+1910pk	243
D(+)-*n*-Pentylthiosuccinic	I	$C_5H_{11}S$	+3750pk	250	+1070pk	244	+5200pk	253	+1735pk	244
D(+)-Hydroxysuccinic (malic) (E)	I	HO	−1240tr	227	−2720!	218	−1590tr	230	−630!	222
D(+)-Methoxysuccinic (E)	I	CH_3O	−735tr	227	−3540!	222	−740tr	231	−3275!	222
D(+)-Ethoxysuccinic (E)	I	C_2H_5O	−820tr	227	−3420!	222	−715tr	232	−3065!	222
D(+)-*n*-Propoxysuccinic (E)	I	C_3H_7O	−700tr	227	−3010!	222	−705tr	231	−2805!	222
(+)-*trans*-Caronic	V		+5010pk	231	+5440pk	230	+4400pk	230	+5750pk	231

reached in most cases, and for alkylsuccinic acids (I; R = alkyl) it has been shown that compounds of the D- and L-configurations (for nomenclature see Linstead *et al.*[4]) have positive and negative Cotton effects, respectively. Using the sequence rule,[5] D = R and L = S.

It has previously been shown that (+)-methylsuccinic acid has the D-configuration by use of the quasiracemate method and also by relating it to mercaptosuccinic acid and malic acid. The various alkylsuccinic acids have then been correlated by quasiracemate formation between adjacent members of the series.[6] The fact that all (+)-alkylsuccinic acids have now been shown to give positive Cotton effects confirms these previous correlations.

The alkylsuccinic acids show a steady increase in molecular rotation at the first extremum as the alkyl group increases in bulk from methylsuccinic acid to cyclohexylsuccinic acid, apart from the isopropyl derivative which has a molecular rotation of +2470 at the peak. This figure is very similar to the value of +2400 for cyclohexylsuccinic acid, a comparison which may reflect the influence of branching in a side-chain immediately adjacent to the asymmetric centre (cf. II and III).

TABLE 2

Ultraviolet absorption spectra of some monosubstituted succinic acids (in water)

Acid	I; R =	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
Methylsuccinic	Me	203pk	109
Hydroxysuccinic (malic)	HO	203sh	152
Methoxysuccinic	MeO	206sh	170
Methylthiosuccinic	MeS	238pk 202sh	435 1860
Bromosuccinic	Br	220sh	590

Arylsuccinic Acids.—Some arylsuccinic acids of the D-series [7,8] also show positive Cotton effects (Table 1). The magnitude of rotation at the first extremum decreases as the number of methylene groups between the aromatic nucleus and the asymmetric centre increase. (These compounds will be discussed in detail elsewhere.[9]) Aryl groups have an absorption band at about 270 mμ which in some compounds gives rise to Cotton effects in this region. However, the reduction product of D-(+)-α-phenylsuccinic acid [S-(+)-2-phenylbutane-1,4-diol] shows only a very small Cotton effect with a peak ([ϕ] +500) at 239 mμ, as compared with the phenylsuccinic acid itself ([ϕ] +15450) at 231 mμ. This large Cotton effect in the arylsuccinic acids may therefore be ascribed to the carboxyl chromophore.

α-Alkylglutaric Acids.—The results for the succinic acids may be compared with those for monosubstituted glutaric acids (IV). Only two compounds have been examined; D(−)-methylglutaric acid [10] gave a positive rotatory dispersion curve, but the first extremum of the Cotton effect could not be reached. D(−)-Isopropylglutaric acid [IV; R = Pr^{i}] [11] gave a positive Cotton effect, but with a much smaller molecular rotation at the peak than the corresponding compound in the succinic acid series (+555 as opposed to +2470).

Halogenosuccinic Acids.—D(+)-Chlorosuccinic and D-(+)-bromosuccinic acids [12] have also been examined and gave positive Cotton effects, with the first extremum at considerably

---

[4] R. P. Linstead, J. C. Lunt, and B. C. L. Weedon, *J.*, 1950, 3333.

[5] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 1956, **12**, 81.

[6] A. Fredga, *Tetrahedron*, 1960, **8**, 126; A. Fredga, *Arkiv. Kemi, Min. Geol.*, 1949, **26***B*, 11; *ibid.*, 1940, **14***B*, 27; M. Matell, *Arkiv. Kemi*, 1952, **5**, 17.

[7] A. Fredga, *Arkiv. Kemi*, 1953, **6**, 277.

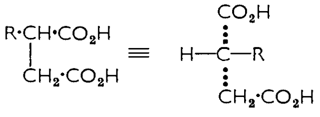
[8] A. Fredga, B. Sjöberg, S. Sjöberg, and M. Zeppezauer, unpublished results.

[9] S. Sjöberg, unpublished observations.

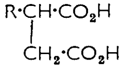
[10] A. Fredga, *Arkiv. Kemi, Min. Geol.*, 1947, **24***A*, 32; V. H. T. James, *Chem. and Ind.*, 1955, 1388; *J.*, 1955, 637.

[11] A. Fredga and J. K. Miettinen, *Acta Chem. Scand.*, 1947, **1**, 371.

[12] M. Centnerzwer, *Z. phys. Chem.*, 1899, **29**, 715; J. Timmermanns, *Rec. Trav. chim.*, 1929, **48**, 890.

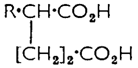


(I) *D*-Configuration



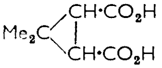
$$\begin{array}{l} R\cdot CH\cdot CO_2H \\ | \\ CH_2\cdot CO_2H \end{array}$$

(II); R = Pr^i
(III); R = cyclohexyl



$$\begin{array}{l} R\cdot CH\cdot CO_2H \\ | \\ [CH_2]_2\cdot CO_2H \end{array}$$

(IV)



(V)

longer wavelengths than for the alkylsuccinic acids. Optically active 2-chloro-octane and 2-bromo-octane (kindly provided by Dr. W. Gerrard, Northern Polytechnic, London) showed no Cotton effect in the region 400—213 mμ, and the observed extrema in the o.r.d. curves of chloro- and bromo-succinic acids may therefore be attributed to the carboxyl chromophore. However, the carboxyl group is clearly influenced by the proximity of a halogen atom as is shown by the positions of the ultraviolet absorption [cf. bromosuccinic acid, $\lambda_{max.}$ 220 mμ (shoulder); methylsuccinic acid, $\lambda_{max.}$ 203 mμ; Table 2].

Alkylthiosuccinic Acids.—The series of *D*-alkylthiosuccinic acids [13] have positive Cotton effects, for which the first extremum occurs at about 248 mμ. n-Propyl- and isopropylthiosuccinic acids each show a second peak at 227 mμ, and the curves for some other members of the series show slight inflections in this region. Circular dichroism measurements with these compounds, for which we are greatly indebted to Professor G. Ourisson and Dr. Lutz, Strasbourg, give similar results for all members of the series (Table 3). The alkylthiols, RSR', have two weak absorption bands in the low wavelength region, with $\lambda_{max.}$ at 230 and 210 mμ and $\varepsilon_{max.}$ 150—1000, respectively. It therefore appears that the Cotton effect of longer wavelength in the o.r.d. curve may be due to the 230 mμ absorption band of the alkylthiol group, and that the second peak at 227 mμ may be due to the combined absorptions of the shorter wavelength alkylthiol band and the carboxyl absorption band at ~215 mμ.

TABLE 3

Circular dichroism of alkylthiosuccinic acids

		First absorption band	
Acid	I; R =	$\Delta\varepsilon_{max.}$	λ (mμ)
D(+)-Methylthiosuccinic	CH_3S	+1·998	235
D(+)-Ethylthiosuccinic	C_2H_5S	+1·62	237—243
D(+)-Propylthiosuccinic	C_3H_7S	+1·773	244
D(+)-Isopropylthiosuccinic	$(CH_3)_2CHS$	+0·92	243—245
D(+)-*n*-Butylthiosuccinic	C_4H_9S	+1·732	239—243
D(+)-*n*-Pentylthiosuccinic	$C_5H_{11}S$	+1·685	237

Hydroxy- and Alkoxy-succinic Acids.—Four members of this series have been examined, *D*(+)-malic acid and its *O*-methyl, *O*-ethyl, and *O*-propyl ethers (for absolute configurations see ref. 14). All give negative Cotton effects in water and in methanol.

Effect of Alkali.—The sign of rotation of simple substituted succinic acids is *reversed* on the addition of alkali, to give a dispersion curve of opposite sign. This has been investigated both for aqueous and methanolic solution and the results are in Table 1. The effect of alkali is most clearly seen for the *D*-alkyl-substituted acids in aqueous solution where the sign of rotation is changed, and negative curves have been obtained in all cases. Isopropylsuccinic and cyclohexylsuccinic acids are distinguished from the rest of the series in that the molecular rotation is smaller numerically than for other compounds; in

---

[13] M. Matell, *Arkiv. Kemi*, 1952, **5**, 17.

[14] A. Lardon and T. Reichstein, *Helv. Chim. Acta*, 1949, **32**, 2003; T. Purdie and G. B. Neave, *J.*, 1910, **97**, 1517; T. Purdie and W. Pitkeathley, *J.*, 1899, **75**, 157.

alkaline methanol solution, these two compounds have small positive curves, whereas the rest of the series have negative rotations.

The first extremum of the Cotton effect occurs at a shorter wavelength in the presence of alkali than for the free acid. This may be compared with amino-acids,[3] where the first extremum occurs at about 225 mμ for $^+NH_3{\cdot}CHR{\cdot}CO_2H$ but about 215 mμ for $^+NH_3{\cdot}CHR{\cdot}CO_2^-$.

Two of these compounds, *D*(+)-ethylsuccinic acid and *D*(+)-cyclohexylsuccinic acid, were investigated in more detail, using varying proportions of alkali and acid (see Table 4).

TABLE 4

Optical rotatory dispersion of monosubstituted succinic acids in alkali

Equiv. KOH per CO_2H grp.	[ϕ] in water at 227 mμ	[ϕ] in methanol at 238 mμ
	(+)-Ethylsuccinic acid	
0	+1710	+1110
0·5	+1110	+725
0·75	−80	+320
1	−1280	−205
2	−1480	−440
4	−1525	−335
6	−1515	−280
12	−1410	−195
	(+)-Cyclohexylsuccinic acid	
	at 222 mμ	at about 222 mμ
0	+2650	+2740
0·4	+2230	+2320
1	−405	+660
2	−785	+360
4	−735	+565
10	−565	+625

(+)-Caronic acid

Equiv. KOH per CO_2H grp.	[ϕ] in water at 231 mμ	[ϕ] in methanol at 231 mμ
0	+5010	+4400
0·5	+5040	+4960
1	+5480	+5640
1·5	+5580	+5875
6	+5440	+5750

The results show that the inverted rotation reaches a maximum after the addition of two equivalents of potassium hydroxide for every carboxyl group, and that further addition of alkali produces no significant alteration in rotation. To ensure that the point of maximum inversion had been reached in studying the entire series of acids, three equivalents of potassium hydroxide were added to each compound. A detailed study was also made of (+)-caronic acid (V) (for absolute configuration see ref. 15). In this compound, the central carbon chain is part of a rigid cyclopropane ring and the bonds joining the two carboxyl groups to this ring are held in one fixed conformation. The value of the molecular rotation at the peak is considerably greater than that for the corresponding acyclic molecule, isopropylsuccinic acid. No significant change in the rotatory dispersion was observed on adding alkali to solutions of caronic acid in water or in methanol, thus confirming that no major change in conformation can occur.

Succinic acids with substituents other than alkyl show a varied pattern of behaviour, in the presence of alkali. The compounds with aryl substituents give curves which are of the same sign as the acid alone, but with smaller numerical values. The *D*(+)-alkylthiosuccinic acids in alkali also have positive Cotton effects but the molecular rotation at the first extremum is only about one third of its value for the free acid.

In the case of the *D*(+)-alkoxysuccinic acids, which have negative Cotton effects in water and in methanol, the sign of rotation is not changed in the presence of alkali. Instead, the numerical value of the rotation increases giving a much steeper negative curve.

Conclusion.—The data presented enable a comparison to be made of the Cotton effects of dicarboxylic acids differing only in one substituent at a single asymmetric centre. Monosubstituted succinic acids of the *D*-configuration have positive Cotton effects when the

---

[15] L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1954, 470; H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 701.

substituent is alkyl, alkylthio, chlorine, or bromine, but negative Cotton effects when the substituent is hydroxyl or amino.[3]

EXPERIMENTAL

Optical rotatory dispersion curves were measured on the Bellingham and Stanley/Bendix-Ericsson automatic recording spectropolarimeter, Polarmatic 62; solvent, methanol or water; l = 0·1 dm.; t = 20—25°; c = 1 mg./ml. or less.

Alkali Treatment.—Solvent, 0·05N-KOH in methanol or water; l = 0·1 dm.; t = 20—25°; c = 1 mg./ml. or less; *ca.* 3 moles alkali/carboxyl group. For detailed studies of optical rotatory dispersion in alkali, the following concentrations were used, either in water or in methanol; (+)-ethylsuccinic acid, 0·02M; (+)-cyclohexylsuccinic acid, 0·01M; (+)-caronic acid, 0·02M; potassium hydroxide, 1·25M. In each case, the calculated quantity of alkali was added to the acid solution (3 ml.) and the whole diluted to 5 ml.

Ultraviolet absorption spectra were measured on a Unicam S.P. 700 spectrophotometer. Solvent, methanol; pathlength = 1 cm.; c = 1 mg./ml. or less.

A. Fredga thanks the Royal Swedish Academy of Science for grants, and Mrs. Maj von Sivers-Jakobsson for experimental assistance. W. Klyne and P. M. Scopes thank the D.S.I.R. for a grant. We thank Miss M.-A. Pulle and Miss C. Snell for technical assistance.

(A. F., S. S.) UNIVERSITY OF UPPSALA, SWEDEN.
(B. S.) A.B. ASTRA, SÖDERTALJE, SWEDEN.
(W. K., J. P. J., P. M. S.) WESTFIELD COLLEGE,
LONDON N.W.3.

[*Received, October 27th,* 1964.]